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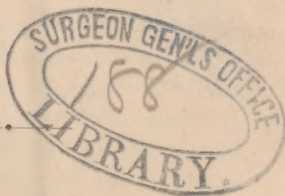
MEDICINAL DOSES

—AND—

Therapeutic Effects.

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Reprint from the DETROIT LANCET, August, 1880.

GEO. S. DAVIS, Publisher.

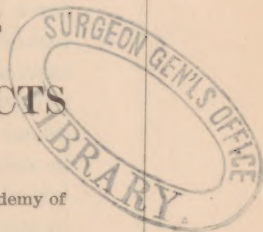
MEDICINAL DOSES AND THERAPEUTIC EFFECTS

BY H. CULBERTSON, M. D.

Mr. President and Gentlemen of the Zanesville Academy of
Medicine:

ONE hundred years ago Hahnemann enun-
ciated his therapeutical law, "*similia
similibus curantur.*" Hippocrates (B. C.
460) had promulgated the same law, but to
the former belongs whatever credit is due in
founding the so-called system of homœo-
pathy. Hahnemann took Peruvian barks,
which he thought produced symptoms of
ague in his own person, and claimed, there-
fore, that cinchona was the remedy for
ague, because it (barks) induced symptoms
similar to those found in ague. That ague
is produced by cinchona is refuted, so far
as its origin from the plant is concerned, by
the researches of Mitchell, Salisbury and
others. The former referred the cause of
this disease to certain cryptogamiæ, the lat-
ter to several forms of the Palmellæ.* We
do not understand Hahnemann as claiming
from his experiments (of which those with
"the barks" were but one) that medicines
act therapeutically from being *identical* in
their nature with the several causes of dis-

*Am. Jour. Med. Sci., N. S., Vol. 51, p. 62.



ease (though this is sometimes affirmed), but that medicinal agents control disease per force of the fact that the agents are not *identical* in nature with the causes of disease, and are yet capable of inducing in the human body similar phenomena to those produced by disease when exhibited. It will be seen then that the foundation of this doctrine lies in the non-identity or the difference in the nature of those causes which produce disease and the character of the agents given to cure maladies. The remedy acts therapeutically, not because it develops an element of similarity to disease, but from the very fact that it reveals the character of non-identity to the traits of disease in its effects. The dogma could not be maintained for a moment, that *identicals would cure identicals*; this would be nonsense. So then, it was held that the nearest approximation to this motto should form the basis of the homœopathic system, viz., "*like cures like.*" But as it is clear that identical causes acting under the same circumstances could not produce different effects, it follows that the causes of disease must be different in nature from that of the remedies given to cure disease. Hence we are driven to the conclusion that the whole remedial power of medicines lies in the fact that the causes of disease and the agents given for their cure are not similar in their nature. Just how medicines act to produce their effects no one can determine—we only know results, first causes are

beyond our scope. Why oil accelerates and opium retards the action of the bowels no one has been able to demonstrate. We rest then upon clinical facts in the cure of disease, as the physicist does upon phenomena, and it is a fact equally palpable, that the homœopathist cannot prove that his cures rest on the law "*similia*," but only that a remedy when given effects the cure he really knows not how. This is only clinical experience. Hahnemann himself did not hold that to cure homœopathically it was absolutely essential that the doses should be infinitesimal, but that such minute doses did not perturbate the general system and served to favor the action of the agent. It is, too, I understand, a fact that modern homœopathy permits the use of medicines in full doses. From these considerations it is evident that there is no true foundation for the system of homœopathy. We may, therefore, hold that the law of "*similia similibus curantur*" will not account for the "*modus operandi*" of medicines upon the animal body, and proceed to the consideration of the histological relations of our subject. What influence does the minute structure of organs exercise in producing the diverse remedial effects observed from medicines in the human body? In endeavoring to solve this query it will be necessary to investigate the characteristic structure of a few of the organs of the body, so far as to consider the connection the nerves have with these.

The Skin—The pacinian corpuscles are composed of a homogeneous nucleated membrane or sheath, within which is a series of laminated structures. The medullated nerves enter the cavity of the innermost capsule, and the axis nerve cylinder now runs to the blind extremity of the capsule and terminates in one or several small tuberosities and is surrounded by the nerve medulla, which fills the cavity of the innermost capsule. A large blood vessel enters near the nerve fibre and forms an abundant capillary net-work between the outer capsules (Biesiadecki).*

Meissner's or Wagner's corpuscles, palpation corpuscles. The medullated nerves enter these, but the manner in which they end within them is not known.†

The non-medullated nerve fibres of the skin terminate in the rete-mucosum, beneath the epithelial layer of the skin, in knob-like distensions.‡

The sensitive nerves of the cornea terminate in the cells of the most superficial layer of its epithelium (Rollett).§

Schultz|| believes that the rods and cones of the retina are the terminal organs of the optic-nerve fibres, and that it is highly probable that the inner and outer segments of these structures have a common envelop, but adds that every other method of continuity

*Stricker's Manual of Histology, p. 550.

†Ibid, p. 551.

‡Ibid., p. 552.

§Ibid., p. 929.

||Ibid., p. 826.

between them, for instance, by interior nervous fibres, is a bare hypothesis. It is clear then that these retinal nervous fibrils have at least an external covering.

Iris—The ultimate termination of the nerves of the iris is not ascertained.¹

Iwanoff² states that the vessels, nerves and muscles of the iris are embedded in a stroma, which consists mostly of connective tissue fibrils and cells.

Organs of Smell—Babuchin³ states that the distribution of the ultimate olfactory fibrillæ after they have reached the epithelial layer is not known. He denies that they reach the surface of the epithelial layers, as in the cornea.

Organs of Taste—Engelmann⁴ states from his investigations that it is highly probable the nerves of taste after entering the “taste buds divide into ultimate fibrils, which are continuous with the central processes of the “taste cells” of the “taste buds.” In the mucous membrane of the tongue are found sensitive nerves which terminate in the papilla, and the ends of the ultimate filaments of which are surrounded by miniature pacinian bodies.⁵

In the stomach the branches from the pneumogastric nerves and from the solar plexus form gangliform plexuses both be-

¹Quain's *Elm. of Anat.*, London, 1876, vol. ii., p. 605.

²Stricker's *Histol.*, p. 858.

³Stricker's *Hist.*, p. 798.

⁴*Ibid.*, p. 783.

⁵Dalton's *Humany Physiology*, 1871, p. 359,

tween the layers of the muscular coat and the submucous coat, the ultimate ending of which has not been traced.⁶

The nerves of the small intestine are chiefly derived from the superior mesenteric plexus. These nerves first form Auerbach's or the muscular plexus. Branches proceed from these and form a second gangliform plexus in the sub-mucous layer or Meissner's plexus. Fibres pass from this plexus to the muscular elements of the mucous membrane proper, while excessively fine fibrils are sent inwards towards the epithelium; but the further course of these filaments has not been traced.⁷

Hering⁸ says that all demonstrable nerves lie outside of the lobules of the liver, and that he has never been able to find them on the inside of the lobules, much less within the liver cells.

Kühne⁹ says that the motor nerves end in the terminal "nerve-plate" beneath the sarcolemma of the muscle cell. This plate is surrounded by granular protoplasm and nuclei. The extremity of the nerve never dips into the interior of the contractile cylinder.

Pflüger¹⁰ holds that the ultimate fibrils of the salivary nerves end in multipolar cells,

⁶Quain's Anat., loc. cit., vol. ii, p. 356.

⁷Quain, loc. cit., vol. ii, p. 368.

⁸Stricker's Hist., p. 427.

⁹Ibid., p. 155.

¹⁰Ibid., p. 307.

and that the latter connect directly with the salivary cells.

According to Schultz,¹¹ it is undecided whether the ultimate fibrils of nerves originate in the ganglion cells, or only pass through these cells by the multipolar processes. It is known, however, that these fibrils enter these grey nerve cells.

Speaking of blood vessels, Eberth¹² says, "with the exception of the capillaries, the presence of nerves has been demonstrated in all vessels," * * * he adds "he has not been able to convince himself of the precise mode in which they terminate."

We may add what is known to be a fact, that there are many structures of the body in which nerves have not been found by the most approved methods of investigation, and that the lining layer of blood vessels has not been shown to contain nerves.

The minute structure of other organs might be considered, but that of a sufficient number of these has been given to show that there are no terminal nervous filaments found absolutely exposed. Even in the cornea its nerves are surrounded by at least the edges of the external epithelial layer and the corneal cement. Nerves of special and common sensation are clothed by some form of investment, so that impressions are not made upon the terminal and exposed nerve ends. Generally the structures about these nerve end-

¹¹Ibid., p. 142.

¹²Ibid., p. 193.

ings are supplied with blood capillaries, through which medicinal substances may pass ere reaching and impressing the ends of nerves. It is possible that medicinal agents might pass through the structures about the nerve ends, without entering the blood vessels by osmosis. But if we consider the stomach, and that its mucous membrane is freely supplied with blood vessels, and that its nerves do not penetrate its epithelial layer, and that sensitive impressions are made upon the terminal extremities of nerves, it is probable that medicinal substances ordinarily enter first the circulation and finally reach the nerve endings after having traversed the rounds of that system.

It may be that some form of remedial influence can be exercised by osmosis taking place through the structures which surround the nerve ends, without entering the general circulation, provided such remedies can pass through these accessory structures without being themselves changed in the transit or modifying these delicate textures. I do not know that such direct transit ever takes place, but it is a fact that atropia introduced subcutaneously will paralyze sensibility; whether this effect is due to the influence of the agent on the peripheral extremity of the nerve, or its action on the ganglia of the spinal cord, is a very difficult question to decide.¹³ We know positively that the sciatic (a motor nerve) can be rendered com-

¹³The Action of Medicines, Isaac Ott, p. 50.

pletely unirritable—its motor irritability killed—by atropine, introduced subcutaneously, while the muscles supplied by it retain their irritability, and that woorari “kills the intra-muscular nerve endings,” “leaving the sensory nerves and sensory ganglia intact.”¹⁴

We know, too, that such agents may be introduced subcutaneously and their paralyzing influence be observed in distant parts of the animal body, showing that such effects have been produced by the agents traversing the rounds of the circulation. On the other hand, if we take a frog, remove the cerebrum, dissect out the gastrocnemii and place one in a 1 per cent. solution of salt and the other in a solution of sanguinaria, it will be found that the latter muscle has lost its irritability from the direct effect of the poison, while the *other* has not. Again, if we expose the ends of the right and left sciatic nerves of a frog, immerse one peripheral extremity in a solution of phosphate of soda, the end of the other nerve in a solution of atropia, “the most that can be said is that the sensory nerves retain their irritability for a considerable time in a 2½ per cent. solution of atropia.”¹⁵ This experiment denotes that the peripheral extremities of nerves may be impressed, though not so readily, as through the medium of the circulation.

If we consider the normal action of these

¹⁴Ibid., p. 50 and 26.

¹⁵Ott, loc. cit., p. 51.

peripheral nerve structures, it is found that "this state of physiological action produces no visible change in the nervous filament itself. Its effects are manifest only at the extremities of the nerve, in the organs in which it has its termination."¹⁶

If no physical change is observed from the physiological action, it is possible none might be detected from the influence of medicines. But it does not follow there should be no change observed from a remedial agency, because none is seen from the operation of the normal functions of the body.

From these considerations and others which might be adduced, it may be fairly claimed, that there are remedies which address their influence to the nervous filaments no matter how they reach these, by circulation or osmosis, directly applied. On the other hand, there are substances which influence remedially parts of the body which do not contain nerves, and hence it is evident that medicines do not act universally through, or primarily upon, the nerves.

I pass now to consider a point connected with this subject, which is probably not often thought upon, viz., the absolute quantity of medicine required to produce a remedial effect. We know on the one hand that enormous portions of agents, recognized as poisons, may be reached and taken with impunity through habit. On the other hand, the phases of idiosyncrasy develop how

¹⁶Dalton's *Physiol.*, p. 381.

minute quantities of remedies may produce overwhelming effects. Thus, for instance, the 1-50 of a grain of strychnia used hypodermically for the first time (I understand, in an adult), has caused convulsions and insensibility, which continued several hours.¹⁷ Let us look at this dilution. If this patient weighed 150 lbs. avd., and the blood weighed 18 lbs. = 126,000 grains avd., then, in this case, a poisonous effect has been produced by the diffusion of the $\frac{1}{50}$ of a grain of strychnia in 126,000 grains of blood, or a dilution of the $\frac{1}{6300000}$. It is true that up to a certain point, and until excretion of the agent begins to diminish the quantity in the circulation, the effect of the poison is increased by the continual presence of new portions of the agent at a given point, brought thither by the circulation. If we assume that the strychnia was equally diffused throughout the blood, and that the blood circulates every three minutes, then during the two hours that the effects of the remedy lasted a given ganglionic cell of the spinal cord would be impressed by the poison forty times, thus increasing the effect forty fold, which is equivalent to a dilution of $\frac{1}{1575000}$. Again, the effect of the poison is no doubt increased by the simultaneous influence it exercises upon the millions of gray nerve-cells of the nervous system, which are more or less intimately connected with each other. Thus considered, if there

¹⁷Taylor on Poisons, 3d Am. ed., p. 71.

were a million of such cells, and a $\frac{1}{1000000}$ of a grain of the agent impressing each cell the effect would hypothetically equal the influence of *one* grain upon *one* gray cell. It is extremely probable that this hypothesis is true to a certain extent, and if so, it goes far to account for the wonderful influence of certain agents upon the body.

It is not astonishing, then, that half a grain of strychnia has destroyed the life of an adult in 20 minutes.¹⁸ Here the $\frac{1}{252000}$ part of this substance impressed each nerve cell, producing an effect which overcame the vital forces of the nervous system and induced the death.

Two grains of arsenic have produced death in an adult; that is, $\frac{1}{63400}$ part in 1 part of blood acting upon the numerous cells of the body, has induced this result.

The effect of medicinal agents illustrates often how potent the remedial influence is in small doses. Thus, atropine and digitaline given internally in $\frac{1}{60}$ grain doses will produce distinct effects. This is a dilution of $\frac{1}{7560000}$. Again arsenic in $\frac{1}{16}$ grain doses will induce remedial results, a dilution of $\frac{1}{3016000}$. Again, eight drops of tr. verat. virid. will provoke nausea. If in this amount of the tincture there is $\frac{1}{40}$ grain of the alkaloids of the plant, then the remedial agency would accrue from a dilution of $\frac{1}{5040000}$ of a grain.

It may be that these several effects are

¹⁸Taylor on Poisons, loc. cit., p. 60.

brought about, in a certain degree, by particular portions of the cell structure of the spinal cord being peculiarly susceptible to the influence of the agents, and thus the action of these becomes more potent in its effects.

When remedies are prescribed by the homœopathist and infinitesimally according to his therapeutical belief, the attenuation in the blood, of the remedy, is beyond our comprehension. So great is this dilution that no one can comprehend how remedies so attenuated can possibly influence the body. To illustrate: If we dilute a dose of atropine, $\frac{1}{60}$ of a grain, a million times, we will have $\frac{1}{60000000}$ of a grain as a so-called homœopathic dose of this agent. But this hypothetical quantity must be further attenuated in the 126,000 grains of blood, and hence, one grain of blood will contain but the $\frac{1}{9560000000000}$ (the one nine trillion 560 billionth) part of a grain, and which it is claimed will produce a medicinal effect. Common sense and the dictates of reason reveal the absurdity of the conclusion that such a quantity can induce even an imaginary influence.

The therapeutical results cited lead to the consideration of the importance of a resort to reasonably small doses of medicines, as well as the necessity of physicians in the practice of their profession, using concentrated remedies and the alkaloids.

It is not to be denied, however, that, in

many instances, large doses of medicines are demanded to secure remedial effects; as tannin in hæmorrhage, and quinia in severe malarial paroxysms. The former may act by coagulating the fluids about the bleeding vessels, and the latter is thought to diminish the calibre of the capillaries. Opium, too, though demanded only in small doses, constricts the finer blood vessels, probably by its influence upon the vaso-motor system of nerves, and derived from the ganglionic nerve centres. But Bence Jones¹⁹ claims that this remedy may act upon the nerve-cells of the nervous masses, by uniting with the *protogon* of these cells for a time, which constitutes the duration of the medicinal influence, then this union ceasing, the agent is removed by excretion.

I need not further consume the time of the Society with this subject. Enough has been said to denote that the mode of action of therapeutic agents is not uniform, that it is possible remedies may act primarily upon the nervous system, upon the vascular, or upon the intima of organic cells. Further, the smallness of medicinal doses has been mentioned—how minute quantities may act remedially; and it has been distinctly claimed that when remedies act in such minute portions, or in any quantity, that they are not efficient upon the law of “*similia similibus curantur*,” and that this law will not lead to successful therapeutics.

These few remarks are rather suggestive than authoritative, and are submitted to the members hoping they will lead to reflection upon the intricate subject of “medicinal doses and therapeutical effects.”

ZANESVILLE, O., May 6th, 1880.

¹⁹Braith. Retrospect, Am. ed., January, 1867, p. 229.